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Molecular Transport Through Channels and Pores

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Facilitated translocation of molecules through channels and pores is of fundamental importance for transmembrane transport in biological systems. Several such systems have specific binding sites inside the channel, but a clear understanding of how the interaction between channel and molecules affects the flow is still missing. We present a generic analytical treatment of the problem that relates molecular flow to the first passage time across and the number of particles inside the channel. Both quantities depend in different ways on the channel properties. For the idealized case of non-interacting molecules we find an increased flow whenever there is a binding site in the channel, despite an increased first passage time. In the more realistic case that molecules may block the channel, we find an increase of flow only up to a certain threshold value of the binding strength and a dependence on the sign of the concentration gradient, *i.e.* asymmetric transport. In all cases the reason for transport facilitation is an increased occupation probability of a particle inside the channel that overcomes any increase in the first passage time due to binding.

1 Introduction

Diffusion of molecules through channels and pores of an otherwise impermeable membrane is an important issue in biological transport at the cellular level[1,2]. In recent years it has been noted that there are several cases where the molecules transported interact strongly with regions inside the channel[3–7], apparently leading to an increase in transmembrane transport.

From an intuitive point of view, it is not clear at all why a strong interaction with the channel should facilitate transport. Indeed, one would expect that a strong binding is associated with a longer residence time inside the channel which reduces flow. Furthermore, molecules bound temporarily inside the channel may hamper transport of other molecules, especially when they are large[5], and block the channel. So, why do traps and/or reaction sites within the channel facilitate molecular flow? These questions have to be addressed in the generic biological setting of a macroscopic concentration gradient across the membrane, see Fig. 1. An appropriate quantitative description should give the flow for a given concentration difference depending on the potential and other parameters describing the molecule-channel interaction. Physical insight can be gained if the flow can be related to other global properties of the system in question.

2 Theory

The dynamics of the density of the molecules inside the channel, $\rho(x,t)$, is determined by the Smoluchowski equation[8],

$$\partial_t \rho(x,t) = D\partial_x \left[\partial_x - F(x)\right] \rho(x,t) \ , \tag{1}$$

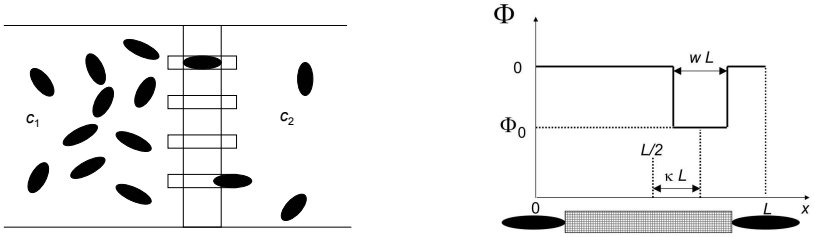

Figure 1. (*left*) Basic biological situation: A membrane separates two baths with molecular concentrations c_1 and c_2. The baths are connected by channels (hatched rectangles) allowing only access of a single molecule. (*right*) Rectangular (box-like) shaped attractive potential of molecule-channel interaction. w is the relative width of the potential well, $|\Phi_0|$ is its depth. The relative shift of the well from its symmetric position is denoted by κ.

where x is the channel coordinate and D is the diffusion coefficient. $F(x)$ is the force describing the molecule-channel interaction that can always be derived from a potential function in one dimension, $F(x) = -\Phi'(x)$. At the ends of the channel we assume that baths hold the molecular densities constant at $\rho(0,t) \equiv c_1$ and $\rho(L,t) \equiv c_2$, respectively, as seen in Fig. 1.

Extending an old approach by Hardt[9] we have shown recently[10] that in this as well as in more general situations the flow J of non-interacting particles across some region is given by a macroscopic version of Fick's law

$$J = \frac{n}{\tau}\,(c_1 - c_2) \tag{2}$$

where τ is the mean first passage time (MFPT) to cross the region[8] and n is a measure of the stationary state particle number in that region.

3 Results

The interplay between specific particle number and first passage time is illustrated by the rectangular potential well of depth Φ_0 sketched in Fig. 1 (*right*).

3.1 Non-Interacting Particles

Using the channel average $\langle . \rangle = L^{-1} \int_0^L dx$ we obtain the results[11]

$$\tau = \frac{L^2}{2D} \langle e^{\Phi} \rangle \langle e^{-\Phi} \rangle \quad , \quad n = \frac{L}{2}\,\langle e^{-\Phi} \rangle \tag{3}$$

for MFPT and specific particle number, respectively. These results have important consequences for any form of the channel potential. Using the Cauchy-Schwarz inequality in the form $\langle f \rangle \langle g \rangle \geq \langle \sqrt{fg} \rangle^2$ on Eq. (3), we immediately see that *any* form of in-channel interaction that is non-constant leads to an increase in the MFPT, $\tau \geq L^2/2D$, and by this hampers particle flow. The physical reason is that potential barriers as well as potential wells have walls, and the particles have to get over these walls irrespective of whether they belong to wells or barriers. That is reflected also in the invariance of τ upon changing barriers to wells and vice versa by setting $\Phi(x) \to -\Phi(x)$. On the other hand, the specific

particle number increases only for predominantly attractive potentials, *i.e.* if the potential wells overcome the effects of barriers in Eq. (3). Both effects conspire to give the total flow as

$$J = \frac{D}{L}\langle e^{\Phi}\rangle^{-1}\,(c1 - c2) \tag{4}$$

So, for fully attractive potentials, *i.e.* $\Phi(x) \leq 0$, we always find an increase of the flow when compared to $\Phi(x) = 0$.

3.2 Blocking the Channel

The approach presented above can be readily extended to describe the effect of molecules that block the channel. As an extreme case we assume in the following that only a single molecule can occupy the channel, which is realistic in many cases. Before, the quantity $\rho(x,t)$ was the density of molecules in the channel at position x. We now interpret $\rho(x,t)$ as the *probability density* that a channel contains a particle at x. It is obvious that this density follows the same dynamics as described above in Eq. (1). However, the state variable x does not completely describe all states, but the empty channel has to be added as an additional state. This additional empty channel state leads to a *cyclic state model* described in more detail in Ref.[11].

Figure 2 (*left*) shows the relative increase of the flow, J/J_0, for a particular set of parameters of a symmetric channel potential. Increase and subsequent decrease of the flow with increasing binding strength (negative Φ_0) can be seen clearly.

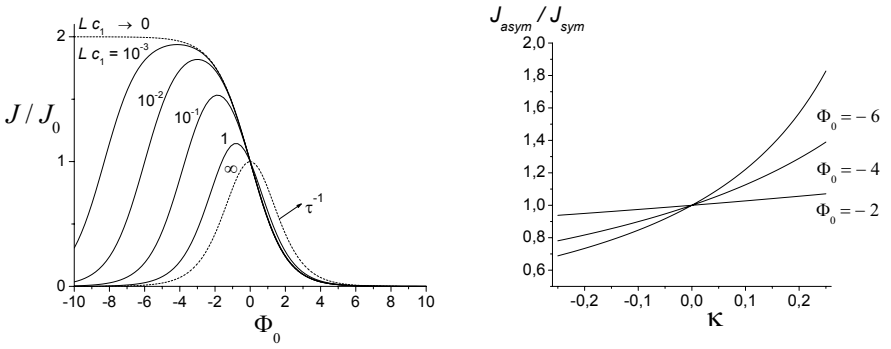

Figure 2. (*left*) Effect of the molecular channel interaction on flow. J_0 refers to vanishing interaction. The potential is box-like shaped, see Fig. 1 (*right*), and assumed to be centered ($\kappa = 0$) with relative width $w = 1/2$. $\Phi_0 > 0$ denotes a barrier and $\Phi_0 < 0$ is an attractive potential, *i.e.* a potential well. Unidirectional flow is considered, *i.e.* c_2 is set to zero, and the concentration c_1 is varied. The limiting cases of vanishing and very high concentration are also considered (dotted lines). Note that for the latter, flow is proportional the inverse first passage time τ. (*right*) Dependence of flow J_{asym} on the position of the binding site, κ, see Fig. 1 (*right*). J_{sym} is the flow for the symmetric potential ($\kappa = 0$). The parameters used are $Lc_1 = 0.1$, $c_2 = 0$, and $w = 1/2$, *i.e.* κ can vary from $-1/4$ to $1/4$. The flow increases when the binding site moves from the cis to the $trans$ position with respect to the larger concentration.

The typical behavior of asymmetric transport through the channel, *i.e.* $\kappa \neq 0$, is illustrated in Fig. 2 (*right*) for a particular set of parameters. We see that flow is decreased if the binding site is close to the larger concentration, while the flow is increased otherwise.

Intuitively, flow increase due to the binding site being in the *trans* position, *i.e.* away from the higher concentration, can be viewed as the binding site "pulling" the molecules across the channel. Since in the blocking situation only one molecule is in the channel, exiting to the lower concentration side is faster than diffusing all the way back.

Note that this behavior is a major difference from the idealized case of non-interacting particles, where asymmetry did not matter for the transport. Interestingly, such a directional behavior has been observed most recently in the channel protein OmpF[7].

4 Concluding Remarks

We presented an analytical approach to describe molecular transport through a membrane channel in the biological setting of a macroscopic concentration gradient across the membrane as depicted in Fig. 1. The goal was, in particular, to understand whether and how binding sites in a channel can facilitate transport, to understand the effect of channel blocking, and to explore asymmetric transport.

Transport facilitation could be explained by the fact that increased occupation probability inside a channel outweighs any slowing down of channel crossing. Previous approaches to describe asymmetric transport used the *flashing ratchet* paradigm[12]. That approach, however, depends on non-equlibrium fluctuations[13], while the only non-equilibrium aspect of the biological situation in Fig. 1 is the concentration gradient. What came as a surprise to us is that already at this level we were able to also explain asymmetric transport as a side effect of channel blocking. This is of particular importance in the light of recent experimental findings[7].

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